Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-33 and 35-42 are pending in the application, with claim 1 being the independent claim. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Rejections Under 35 U.S.C. § 103

Claims 1, 2, 8, 13, 14, 17-20, 28, 36, and 38-41 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Rossi *et al.*, U.S. Patent No. 5,144,019 (the '019 patent), in view of Wu *et al.*, U.S. Patent No. 5,166,320 (the '320 patent), and Hirsch *et al.*, U.S. Patent No. 5,428,132 (the '132 patent). Applicants respectfully traverse the rejection.

A. The combination of Rossi et al., in view of Wu et al. and Hirsch et al. fails to suggest or motivate one of ordinary skill in the art to make the claimed invention.

According to the Examiner,

> [t]he '019 patent [Rossi *et al.*] teaches targeting HIV infected T cells with liposomes carrying ribozymes.
>
> The claimed invention differs from the prior art by using antibody-polycation-ribozyme conjugates to target T cells for treating HIV. However, the '320 patent [Wu *et al.*] specifically teaches that liposome polynucleotide delivery systems are problematic because there has been difficulty in directing cell type specificity (column 1, lines 50-52 in particular). The '320 patent teaches overcoming this problem by creating a polynucleotide delivery system that links the polynucleotide of interest to a polycation and then links the polycation to a specific cell receptor binding ligand, such as an antibody. The '132 patent [Hirsch *et al.*] teaches targeting T cells by using an antibody to CD3 (see column 4, lines 45-48 in particular).

Therefore one of skill in the art at the time the invention was made would have been motivated to substitute the liposome-ribozyme delivery system taught by the '019 patent to infect HIV infected T cells with an antibody polycation polynucleotide delivery system taught by the '320 because the antibody polycation polynucleotide delivery systems have cell specificity while liposome-polynucleotide conjugate do not. Furthermore, it would have been obvious to use the anti-CD3 antibodies taught by the '132 patent, since anti-CD3 antibodies specifically target T cells and said anti-CD3 antibodies are specifically taken up by T cells.

Rossi *et al.*, having a 35 U.S.C. § 102(e) date of June 21, 1989, do not teach or suggest that its method has problems. As the Examiner has suggested, Wu *et al.*, having a 35 U.S.C. § 102(e) date of April 22, 1987, which is *before* the 35 U.S.C. § 102(e) date of Rossi *et al.*, do teach that liposome gene delivery systems have "inherent problems" and that the object of their invention is to provide "new and improved carrier system[s]." Col. 1, lines 46 and 56. However, Wu *et al.* provide no comparative data which demonstrates that their claimed methods and compositions are superior to other gene-delivery methods. They also do not provide that their gene-delivery method works for introduction of DNA into T-cells. That the system works for select applications in hepatocytes is the full extent of the teaching in Wu *et al.*

To indicate that there are general disadvantages associated with the use of one type of gene-delivery method does not provide a suggestion to utilize another type of method. The state of the art was such that virtually all gene delivery systems were characterized by some problems. *See, e.g.*, Verma, I.M. & N. Somia, *Nature 389*:239-42 (1997) (Exhibit A); Anderson, W.F., *Nature 392(Supp.)*:25-30 (1998) (Exhibit B).

Also, even if one particular method (e.g., antibody-polylysine-polynucleotide conjugates) is *generally* deemed superior to another (e.g., liposome-mediated gene delivery)

by those skilled in the art, that does not necessarily mean that particular method is more advantageous for a *particular* application and that it would not have certain disadvantages in particular applications. *See id.* *See also* Hodgson, C.P., *Bio/Technology 13*:222-25 (1995) (Exhibit C). Nowhere in Rossi *et al.*, Wu *et al.* or Hirsch *et al.* is there a teaching or suggestion that ligand-polycation conjugates would be effective for the problem of delivering and introducing genes into cells of the T-cell lineage. "A general incentive does not make a particular result obvious, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). Because there is no particular teaching that leads one of ordinary skill in the art to arrive at the claimed invention, Applicants assert that the claimed compositions and methods are not obvious.

B. Even assuming, arguendo, that in delivering ribozymes to T-cells, one skilled in the art were to be motivated to look for delivery systems other that those mediated by liposomes, there were many other delivery systems in the art, and Hirsch et al. teach away from the claimed invention.

Assuming, *arguendo*, that in delivering ribozymes to T-cells, one of ordinary skill in the art were to look for gene-delivery systems other than those mediated by liposomes, there is nothing in Rossi *et al.* that would lead one to the ligand-polycation-polynucleotide system of Wu *et al.* Rossi *et al.* teach that alternatives to the liposome-mediated ribozyme delivery methods are cellular transfection methods, calcium phosphate methods, lipofection, electroporation, or the use of a retroviral vector. Col. 6, lines 65-67. Other gene delivery systems known in the art included, for example, DEAE Dextran, cell fusion, gene-gun delivery systems, naked DNA delivery systems, microinjection delivery systems, microbombardment delivery systems, and the antibody-DNA conjugate system of Hirsch

et al. From a myriad of gene delivery systems, there was no motivation for one of ordinary skill in the art to choose the system of Wu *et al.* to deliver ribozymes to a cell.

Given that both Wu *et al.* and Hirsch *et al.* teach gene delivery systems using non-covalent interaction between the DNA and delivery moiety, one of ordinary skill in the art would have been equally motivated to use the Hirsch *et al.* system - an antibody-DNA conjugate, not the Wu *et al.* system - a ligand-polycation-DNA conjugate. This is because the Hirsch *et al.* system requires less components (does not require a polycation component as by Wu *et al.*), specifically describes *successful* targeting of DNA to T-cells (whereas Wu *et al.* do not teach that their system would work for targeting T-cells), and describes a more current work. (Wu *et al.* has a 35 U.S.C. § 102(e) date of April 22, 1987, whereas Hirsch *et al.* has a 35 U.S.C. § 102(e) date of October 11, 1987, and thus Hirsch *et al.* qualifies as a subsequent "publication" to Wu *et al.*) In other words, Hirsch *et al.* teach away from the claimed invention of a ligand-polycation-DNA conjugate!

C. At the priority date of the captioned application, one of ordinary skill in the art would not have had a reasonable expectation of success of making and using the claimed invention.

The Examiner has also asserted that one of ordinary skill in the art would have an expectation of success in combining the documents in order to obtain the claimed invention because antibody conjugating methods were known in the art and methods of linking polynucleotides to polylysine were known in the art. Assuming, *arguendo*, that the cited documents suggested the claimed invention (which they did not), there was no reasonable expectation by one of ordinary skill in the art that the claimed composition would be taken up by cells expressing T-cell surface antigens. Rossi *et al.* provide no indication that

ribozyme genes could be delivered to T-cells using polycation-protein conjugates. Wu *et al.*, while providing experimental data for targeting hepatocytes using asialoglycoproteins, provide no indication that their gene-delivery method would be effective for targeting cells of the T-cell lineage using T-cell receptor-specific antibodies. Hirsch *et al.*, while teaching antibody-DNA conjugates, provide no indication that the addition of a polycation (which can dramatically increase the surface area, weight and volume of the conjugate) could produce conjugates capable of introducing DNA into cells. As is known by those having ordinary skill in the art, the optimal methods of transfecting cells must be determined empirically on a case-by-case basis because each type of cell responds differently to the methods chosen, hence the multitude of methods and compounds utilized for gene transfer in the art.

For example, certain cell surface binding sites may lead to vacuolization and degradation of the nucleic acid within lysozymes. In addition, depending on the state of the cell, certain receptors may be down-regulated resulting in a reduced number of receptors available for targeting. If the goal of transfection was introducing as much foreign DNA as possible to the target cell, one skilled in the art would likely avoid targeting these down-regulated receptors. Also, it was known in the art that HIV infection of T-cells causes a loss of CD4 from cell surfaces via Nef, which acts by inducing CD4 endocytosis. *See* Aiken, C. *et al.*, *Cell 76*:853-64 (1994) (Exhibit D). Thus, one of ordinary skill in the art would recognize that the broad and general teachings of Wu *et al.* would not be completely applicable to all cell types and all cell surface targets, particularly in the transfection of HIV-infected T-cells using CD4 as a target.

Applicants assert that the Examiner has "selectively culled" together known elements from the prior art despite the fact that there is no motivation to do so or expectation of

success in doing so. As discussed, there is no *particular* teaching or suggestion in any of the documents that would motivate one skilled in the art to combine the other documents to arrive at the claimed invention and there is no expectation of success from the prior art that the compositions of the claims would be effective for introduction of genes cells of the T-cell lineage. Thus, Applicants assert that the Examiner has engaged in improper hindsight reasoning gleaned from the captioned application to arrive at the claimed invention.

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

II. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 8-10, 13, 14, 17-20, 28, 29, 36, and 38-41 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly for lack of written description. The Examiner stated that "Applicant has no written support for the sub-genus of the protein component of the conjugate [that] is capable of binding to a cell surface protein other than a transferrin receptor in the originally filed claims or specification." Applicants respectfully traverse the rejection.

In *In re Johnson*, 194 USPQ187, 195 (CCPA 1977), the issue was whether after exclusion from the original claims of two species specifically disclosed in the specification by provisos, the specification satisfied 35 U.S.C. § 112, first paragraph. The Court of Customs and Patent Appeals held that the specification satisfied § 112, first paragraph, with respect to the claims. *Id.* at 196. The court reasoned that "[i]t is for the inventors to decide what *bounds* of protection he will seek." *Id.*

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous

> species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. All that happened here is that appellants narrowed their claims to avoid having them read on a lost interference count.

Id. See also, In re Driscoll, 195 USPQ 434 (CCPA 1977). Copies of the cases attached herewith for the Examiner's convenience as Exhibits E and F.

Similarly, claims 1, 2, 8-10, 13, 14, 17-20, 28, 29, 36, and 38-41 recite that the conjugate is capable of binding to a cell surface protein other than a transferrin receptor expressed by a cell of a T-cell lineage. The specification, in the paragraph bridging pages 4 and 5, describes a transferrin-polycation/DNA complex. Legally, Applicants may decide the bounds of the claimed invention. It is respectfully requested that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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Attachments

Exhibit A:	Verma, I.M. & N. Somia, *Nature 389*:239-42 (1997)
Exhibit B:	Anderson, W.F., *Nature 392(Suppl)*:25-30 (1998)
Exhibit C:	Hodgson, C.P., *Bio/Technology 13*:222-25 (1995)
Exhibit D:	Aiken, C. *et al.*, *Cell 76*:853-64 (1994)
Exhibit E:	*In re Johnson*, 194 USPQ187 (CCPA 1977)
Exhibit F:	*In re Driscoll*, 195 USPQ 434 (CCPA 1977)

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